ORIGINAL ARTICLE

# Increasing Prevalence of Multidrug-Resistant *Streptococcus pneumoniae* in the United States

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In the United States, *Streptococcus pneumoniae* is the most commonly identified bacterial cause of meningitis,[1] otitis media,[2,3] and community-acquired pneumonia,[4] and it is a frequent cause of bacteremia. In the past, approximately 80 percent of patients hospitalized with bacteremic pneumococcal infections died of their illness.[5] With effective antimicrobial agents, mortality has decreased but remains at nearly 20 percent for bacteremic disease in elderly adults.[5,6]

*S. pneumoniae* strains that had a high level of resistance to penicillin and other antimicrobial agents appeared in the United States in the early 1990s.[7] The emergence of *S. pneumoniae* with antimicrobial resistance is a matter of major concern. Treatment failures due to drug resistance have been reported with meningitis[8,9] and otitis media[3,10-12]; the relation between drug resistance and treatment failures among patients with pneumococcal pneumonia is less clear.[13-18]

The Centers for Disease Control and Prevention (CDC) and several state health departments established the Active Bacterial Core Surveillance program as a population-based surveillance system designed to study the epidemiologic features of invasive pneumococcal infections in the United States and to improve tracking of drug-resistant strains. In this report we present data and assess trends in antimicrobial resistance among pneumococcal isolates that cause invasive disease.

## METHODS

### Isolates

In 1998, the Active Bacterial Core Surveillance program monitored invasive pneumococcal infections in greater Portland, Oregon (three counties; estimated 1998 population, 1.4 million); San Francisco County, California (population, 0.7 million); greater Minneapolis and St. Paul (seven counties; population, 2.5 million); greater Baltimore (six counties; population, 2.4 million); greater Atlanta (eight counties; population, 2.8 million); five counties in Tennessee (population, 2.2 million); greater Rochester, New York (seven counties; population, 1.1 million); and the State of Connecticut (population, 3.3 million). The total population under surveillance for 1998 was 16.5 million. All sites except greater Rochester began surveillance on or before July 1, 1995; we excluded data from greater Rochester from analyses of trends over time.

A case of invasive pneumococcal disease was defined by the isolation of *S. pneumoniae* from a normally sterile body site (e.g., blood, cerebrospinal fluid, peritoneal fluid, joint fluid, or pleural fluid) from a resident of the surveillance area during 1995 through 1998. To identify cases, surveillance personnel periodically contacted all clinical microbiology laboratories in their areas. Audits of laboratory records were conducted every six months to ensure complete reporting. Surveillance personnel collected information on patients by means of a standardized questionnaire that included demographic data, information on clinical characteristics, and disease outcome.

### Testing

Pneumococcal isolates were sent to reference laboratories for susceptibility testing by broth microdilution according to the methods of the National Committee for Clinical Laboratory Standards (NCCLS).[19] The isolates from Georgia were tested at the CDC, and starting in 1997, the isolates from Minnesota were tested at the Minnesota Department of Health Laboratory. All others were tested at the University of Texas Health Science Center at San Antonio. In 1998, all three reference laboratories used susceptibility-testing panels that included penicillin, amoxicillin, cefotaxime, cefuroxime, meropenem, erythromycin, clindamycin, chloramphenicol, vancomycin, rifampin,

levofloxacin, tetracycline, trovafloxacin, and quinupristin–dalfopristin. Analyses of trends over time were not possible for amoxicillin, cefuroxime, and quinupristin–dalfopristin, because of changes in panel composition. In 1998, levofloxacin and trovafloxacin were substituted for ofloxacin, which was used from 1995 to 1997. Serotyping with use of the quellung reaction was performed at the CDC and at the Minnesota Department of Health Laboratory.

Isolates were defined as susceptible, having intermediate resistance, or highly resistant to the agents tested according to the NCCLS definitions.[20] We defined an isolate as "resistant" for this analysis if it had either an intermediate or a high level of resistance. In analyses of resistance to multiple drug classes, we grouped the penicillins, cephalosporins, and meropenem into one drug class; isolates resistant to any of these agents (penicillin, amoxicillin, cefotaxime, cefuroxime, or meropenem) were considered resistant to antimicrobial agents of the β-lactam class. Ofloxacin, levofloxacin, and trovafloxacin were grouped as fluoroquinolone agents; other agents were considered to belong to their own drug classes.

### Statistical Analysis

Statistical analyses were conducted with SAS software (SAS Institute, Cary, N.C.) or Epi Info[21] statistical software. Cumulative incidence rates were calculated for the calendar year 1998 with use of projections of the 1998 population from the Census Bureau. We used the chi-square test to compare proportions and the chi-square test for trend for temporal analyses.

We determined odds ratios for groups at risk for infection by penicillin-resistant organisms in 1998 with the use of multivariable logistic-regression modeling. For this analysis, we included all cases identified in 1998 for which penicillin-susceptibility results were available. The models included penicillin susceptibility or resistance as the dichotomous outcome variable and used demographic and clinical variables from the surveillance case-report form as independent variables. We assessed collinearity and interaction among variables in the final multivariable model. P values of less than 0.05 were considered to indicate statistical significance in all analyses.

## RESULTS

### 1998 Surveillance Results

During 1998, 4013 cases of invasive pneumococcal disease were reported; isolates were available for susceptibility testing for 3475 (87 percent; range, 81 percent to 97 percent of isolates from each reporting site). Most isolates came from blood (98 percent). The cumulative incidence of invasive pneumococcal disease for calendar year 1998 ranged from 21 cases per 100,000 population in Tennessee to 33 cases per 100,000 population in California. After adjustment according to the age and race distribution of the U.S. population, the overall cumulative incidence was 23 cases per 100,000 population.

The majority of isolates (65 percent) were susceptible to all the agents tested; the percentage with such susceptibility ranged from 54 percent in Tennessee to 73 percent in New York State. The proportion of isolates that were resistant to at least three drug classes was 13 percent (range, 5 percent in New York to 24 percent in Georgia).

Overall, 24 percent of isolates from 1998 were resistant to penicillin (minimal inhibitory concentration [MIC], ≥0.12 μg per milliliter). The proportion of penicillin-resistant isolates was highest in the two sites in the southeastern United States — Georgia (33 percent) and Tennessee (35 percent) — and lowest in California (15 percent) and New York (15 percent) (Table 1). Isolates with a high level of resistance to penicillin (MIC, ≥2 μg per milliliter) were more common than isolates with intermediate resistance (MIC, 0.12 to 1 μg per milliliter) (14 percent vs. 10 percent).

**TABLE 1**

Factors Independently Associated with Invasive Disease Due to S. pneumoniae with Resistance to Penicillin among All Patients with Invasive Pneumococcal Disease, 1998.

Erythromycin-resistant isolates (MIC, ≥0.5 μg per milliliter) were also most common in Tennessee (22 percent) and Georgia (27 percent) and accounted for 15 percent of isolates from all sites. Of 3103 isolates with a MIC of 4 μg or less of erythromycin per milliliter, only 7 (<1 percent) were highly resistant to clindamycin (MIC, ≥1 μg per milliliter); of 372 isolates with a MIC of at least 8 μg of erythromycin per milliliter, 102 (27 percent) were highly resistant to clindamycin.

Of all agents tested, resistance to trimethoprim–sulfamethoxazole (MIC, ≥1 μg of trimethoprim and 19 μg of sulfamethoxazole per milliliter) was most common (29 percent of isolates). Very few isolates were resistant to rifampin (1 percent) or quinupristin–dalfopristin (<1 percent); all isolates were susceptible to vancomycin (MIC, ≤1 μg per milliliter). Seven isolates (<1 percent) were resistant to levofloxacin; all were from adults 44 to 83 years of age, and five of these seven (71 percent) were resistant to trovafloxacin. Five of the isolates that were resistant to levofloxacin were also resistant to penicillin, four were resistant to cefotaxime, and two were resistant to erythromycin.

Penicillin-susceptible isolates were likely to be susceptible to most of the other drugs tested (Table 2). Among isolates with an intermediate or high level of resistance to penicillin, significantly more isolates were highly resistant to other β-lactam agents than was the case when the isolates were susceptible to penicillin; the

**TABLE 2**

same was true for erythromycin (P<0.001), trimethoprim–sulfamethoxazole (P<0.001), tetracycline (P<0.001), chloramphenicol (P<0.001), clindamycin (P<0.001), levofloxacin (P=0.007), trovafloxacin (P=0.01), and quinupristin–dalfopristin (P=0.02).

In 1998, 3466 isolates (86 percent of all cases of invasive *S. pneumoniae* disease in 1998) were available for serotyping. Of these, 13 could not be typed; 68 different serotypes were identified among the remainder. Serotype 14 was the most common (18 percent of all isolates) and accounted for nearly one fourth of all penicillin-resistant strains (Table 3). Seven serotypes (6A, 6B, 9V, 14, 19A, 19F, and 23F) accounted for 91 percent of all penicillin-resistant strains. For over half of all isolates of serotype 9A, 9V, 19A, or 35B and approximately one third of all isolates of serotype 6A, 6B, 14, 19F, or 23F, the MIC of penicillin was at least 0.12 µg per milliliter. Six serotypes accounted for 90 percent (413 of 458) of isolates that were resistant to at least three drug classes: serotypes 14 (35 percent), 6B (17 percent), 23F (12 percent), 19F (9 percent), 9V (9 percent), and 6A (8 percent). Serotypes included in 7-valent pneumococcal conjugate vaccine formulations (4, 6B, 9V, 14, 18C, 19F, and 23F) comprised 78 percent of all penicillin-resistant strains and 81 percent and 76 percent of penicillin-resistant strains isolated from persons under five years and five or more years of age, respectively. Serotypes included in the 23-valent pneumococcal polysaccharide vaccine[22] accounted for 88 percent of penicillin-resistant strains; this proportion did not vary according to age group.

Proportion of Pneumococcal Isolates That Were Highly Resistant to Various Antimicrobial Agents According to Their Susceptibility to Penicillin, 1998.

**TABLE 3**

Distribution of Pneumococcal Isolates with Resistance to Penicillin, According to Age Group of Patient and Serotype, 1998.

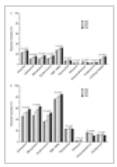
**Factors Associated with Penicillin-Resistant Pneumococcal Disease**

In 1998, penicillin-resistant isolates were more common among strains from children under five years of age (32 percent, vs. 21 percent for persons five or more years of age; P<0.001), whites (26 percent, vs. 22 percent for blacks; P=0.006), and persons from Tennessee or Georgia (34 percent, vs. 19 percent for other sites; P<0.001) (Table 1). In a multivariable logistic-regression model, age group, race, and surveillance area were significantly associated with having a penicillin-resistant isolate (Table 1). After we controlled for these factors, we found no association between the proportion of isolates that were resistant to penicillin and the diagnosis or outcome. On crude analysis, isolates from persons who were not hospitalized were more likely to be resistant to penicillin than isolates from inpatients (27 percent vs. 23 percent, P=0.02); the opposite was true on multivariable analysis after adjustment for other factors.

**Trends in Pneumococcal Resistance, 1995 through 1998**

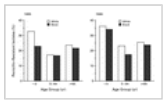
Between 1995 and 1998 (during which period 12,045 total isolates were collected), the proportion of isolates that were resistant to penicillin increased from 21 percent to 25 percent (P<0.001 by chi-square test for trend) (Figure 1A). From 1995 to 1998, the lowest concentration of penicillin that inhibited the growth of 90 percent of pneumococcal isolates ($MIC_{90}$) increased from 1 µg per milliliter to 2 µg per milliliter, and the proportion of isolates for which the MIC of penicillin was at least 4 µg per milliliter increased from 5 percent to 7 percent (P<0.001 by chi-square test for linear trend). In both 1995 and 1998, a higher percentage of whites than blacks in all age groups had a penicillin-resistant infection, although the difference among children under five years of age was smaller in 1998 than in 1995 (Figure 2).

**FIGURE 1**



Frequency of Resistance of Invasive Pneumococcal Isolates to Various Agents According to Year, 1995 through 1998, for Selected Counties in the United States.

**FIGURE 2**



Proportion of Pneumococcal Isolates with Resistance to Penicillin in 1995 and 1998, According to the Patient's Age and Race.

There were also significant increases from 1995 to 1998 in the proportion of isolates that were resistant to many of the other antimicrobial agents tested, including the other β-lactam agents (cefotaxime: from 10 percent in 1995 to 14 percent in 1998, P<0.001; and meropenem: from 10 percent to 16 percent, P< 0.001), erythromycin (from 11 percent to 15 percent, P<0.001), trimethoprim–sulfamethoxazole (from 25 percent to 29 percent, P<0.001), and rifampin (from 0.2 percent to 0.6 percent, P=0.004). These increases occurred exclusively among isolates that were resistant to penicillin (Figure 1B); among penicillin-susceptible strains, we found no increases in the proportion of isolates that were resistant to any of the other agents tested.

There was a decline in the proportion of chloramphenicol-resistant isolates from 1995 to 1998 (from 5 percent to 3 percent, P<0.001) (Figure 1A), which occurred in both penicillin-susceptible and penicillin-resistant strains. Between 1995 and 1997, the overall proportion of isolates that were resistant to ofloxacin increased significantly (from 2.6 percent to 3.8 percent; P=0.01 by chi-square test for trend) (Figure 1A); the amount of increase did not differ between the penicillin-resistant and the penicillin-susceptible isolates. From 1995 to 1998, the overall proportion of isolates that were resistant to three or more drug classes increased significantly (from 9 percent to 14 percent; P<0.001 by chi-square test for trend) (Figure 1A), as did the proportion of isolates that were resistant to amoxicillin, erythromycin, and trimethoprim–sulfamethoxazole, drugs representing three classes of oral agents commonly used as

therapy for otitis media (from 2 percent in 1995 to 9 percent in 1998, P<0.001 by chi-square test for trend).

## DISCUSSION

Between 1995 and 1998, *S. pneumoniae* isolates that were resistant to penicillin became increasingly resistant to other agents (Figure 1B). In 1995, 1 in 11 pneumococcal isolates (9 percent) was resistant to at least three different drug classes; in 1998, that ratio had increased to nearly 1 in 7 (14 percent). Although, in 1998, 65 percent of pneumococcal isolates remained susceptible to all drugs tested, the problem of infections due to multidrug-resistant *S. pneumoniae* is worsening. Because more than one third of isolates are resistant to at least one antimicrobial agent, drug-resistant pneumococci have become a substantial clinical problem. As Table 2 emphasizes, isolates that are susceptible to penicillin are rarely resistant to another agent, whereas isolates that are resistant to penicillin are likely to be resistant to multiple other agents. Choosing an effective therapy for patients with drug-resistant pneumococcal infections is becoming more challenging. Groups of experts have developed treatment recommendations to address the increasing difficulty of treating pneumococcal infections in an era of antimicrobial-resistant strains.[23-25]

Newer-generation macrolides and fluoroquinolones have become popular for treating pneumococcal disease and for the empirical treatment of respiratory infections.[24] Ominously, our data indicate that resistance to erythromycin is increasing among pneumococci, and resistance to the newer macrolides can be inferred from testing isolates for susceptibility to erythromycin.[20,26]

In 1998, resistance to fluoroquinolone agents was uncommon among isolates from our surveillance sites and in other studies.[27-29] From 1995 to 1997, however, there was a 50 percent increase in the proportion of isolates that were resistant to ofloxacin. The increase over time in the proportion of isolates that are resistant to ofloxacin arouses concern that resistance to the other fluoroquinolones will become more common. In a recent report from Canada, investigators found a significant increase in the proportion of pneumococcal isolates from adults for which the MIC of ciprofloxacin was at least 4 µg per milliliter (from none in 1988 and 1993 to 3 percent of isolates in 1997 and 1998).[27] Fluoroquinolone resistance has been found to be due to mutations in the genes encoding subunits of topoisomerase IV (*parC* ) and DNA gyrase A ( *gyrA*).[30] We found that nearly all isolates that were resistant to levofloxacin were also resistant to trovafloxacin; whereas isolates can be resistant to levofloxacin because of a mutation at either the *parC* or the *gyrA* site, mutations in both regions appear to be necessary for isolates to become resistant to trovafloxacin.[31]

Higher proportions of young children and whites had infections due to pneumococcal strains that were resistant to penicillin than was the case among older persons and blacks; this result agrees with those of earlier studies.[7,32] White race is probably a surrogate for factors such as higher socioeconomic status and overuse of antimicrobial agents, which is perhaps more common among whites.[33-35] Between 1995 and 1998, however, the proportion of penicillin-resistant *S. pneumoniae* isolates among strains from blacks under five years of age increased substantially.

From 1995 to 1998, antimicrobial-resistant pneumococci were most common at the surveillance sites in the southeastern United States. In another analysis of Active Bacterial Core Surveillance data, the proportion of resistant isolates varied markedly among institutions in the same area.[36] Geographic variation may be related to the spread of resistant clones, local patterns of antimicrobial use, or other as yet undescribed factors.

A pneumococcal conjugate vaccine has recently become available in the United States for use in young children. Studies indicate that the vaccine is highly effective against invasive disease, and perhaps other syndromes, in young children.[37] Serotypes included in the 7-valent vaccine accounted for 78 percent of penicillin-resistant strains in our study, and if the vaccine provides cross-protection against serotypes 6A and 19A, an additional 15 percent of penicillin-resistant infections would be covered. If the vaccine reduces carriage of vaccine-type pneumococcal strains, as would be expected from the results of trials reported to date,[38,39] we may see a reduction in resistant pneumococci as the vaccine becomes widely used. Even if there is little effect on carriage and transmission, we may see a reduction in the overall proportion of pneumococcal infections that are resistant, because resistant strains are more common in children than in adults. However, whether pneumococci of other serotypes will more frequently become resistant to antimicrobial drugs or replace those included in the conjugate vaccine as major causes of invasive disease remains to be seen.

The CDC's Active Bacterial Core Surveillance is conducted in a population of 16.5 million persons, accounting for nearly 6 percent of the U.S. population. Therefore, analyses of trends in these data can probably be generalized to the U.S. population as a whole. The overall proportion of isolates that were resistant to penicillin was similar to that in other national samples.[28,29,40] One limitation of the surveillance program is that it covers relatively few geographic areas; resistant pneumococci may be a greater or lesser problem in different parts of the United States.

For over a half-century, patients with pneumococcal disease have benefited from penicillin and other antimicrobial agents. Although the majority of strains remain susceptible to all commonly used agents, the increasing prevalence of multidrug-resistant strains illustrates once again the ability of bacteria to survive and adapt. Judicious use of antimicrobial drugs is necessary if we are to avoid

providing a selective advantage for multidrug-resistant organisms. The trend toward greater proportions of pneumococci that have resistance to multiple antimicrobial agents calls for expanded efforts to reduce the unnecessary use of antimicrobial agents and to encourage the use of narrow-spectrum agents. As pneumococcal infections become increasingly difficult to treat, a high priority should be placed on preventing disease by increasing the use of the 23-valent pneumococcal polysaccharide vaccine among high-risk adults and older persons[22] and by use of the new 7-valent conjugate vaccine in children.

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**SOURCE INFORMATION**

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